J Physiol (2003), **550.3**, *pp.* 947–959

DOI: 10.1113/jphysiol.2003.043125
www.jphysiol.org

Journal of Physiology

Spike-dependent intrinsic plasticity increases firing probability in rat striatal neurons *in vivo*

Séverine Mahon*, Guillaume Casassus†, Christophe Mulle† and Stéphane Charpier*

*Chaire de Neuropharmacologie, INSERM U114, Collège de France, 11 place Marcelin Berthelot, 75230 Paris cedex 05 and †Laboratoire de Physiologie Cellulaire de la Synapse, UMR CNRS 5091, Institut François Magendie, Université Bordeaux 2, Bordeaux, 33077 CEDEX, France

The collision of pre- and postsynaptic activity is known to provide a trigger for controlling the gain of synaptic transmission between neurons. Here, using *in vivo* intracellular recordings of rat striatal output neurons, we analyse the effect of a single action potential, generated by ongoing synaptic activity, on subsequent excitatory postsynaptic potentials (EPSPs) evoked by electrical stimulation of the cerebral cortex. This pairing induced a short-term increase in the probability that cortically evoked EPSPs caused striatal cells to fire. This enhanced EPSP-spike coupling was associated with a decrease in the voltage firing threshold with no apparent change in the synaptic strength itself. Antidromic action potentials in striatal cells were also able to induce the facilitation while subthreshold EPSPs were ineffective, indicating that the postsynaptic spike was necessary and sufficient for the induction of the plasticity. A prior spontaneous action potential also enhanced the probability with which directly applied current pulses elicited firing, suggesting that the facilitation originated from changes in the intrinsic electrical properties of the postsynaptic cell. Using whole-cell recordings in cortico-striatal slices, we found that the increase in membrane excitability as well as in EPSP-spike coupling was abolished by low concentration of 4-aminopyridine. This suggests that the intrinsic plasticity results from a time-dependent modulation of a striatal voltage-dependent potassium current available close to the firing threshold. Action potentials thus provide a postsynaptic signal, not only for associative synaptic plasticity but also for activity-dependent intrinsic plasticity, which directly controls the efficacy of coupling between pre- and postsynaptic neurons.

(Received 16 March 2003; accepted after revision 5 May 2003; first published online 4 July 2003)
Corresponding author S. Charpier: Chaire de Neuropharmacologie, INSERM U114, Collège de France, 11 place Marcelin Berthelot, 75230 Paris cedex 05, France. Email: stephane.charpier@college-de-france.fr

Experience-dependent plasticity could result from modifications in synaptic weights between neurons and/or from modulations of membrane excitability of individual cells, which is dynamically controlled by non-synaptic voltage-dependent conductances. Following Hebb's postulate on correlation-based synaptic modifications, it is widely assumed that postsynaptic activity is critically implicated in the induction of associative synaptic plasticity (Linden, 1999; Bi & Poo, 2001). Recent *in vitro* studies (Markram *et al.* 1997; Bi & Po, 2001) have shown that repeated pairings of a postsynaptic spike with excitatory postsynaptic potential (EPSP) result in persistent strengthening or weakening of synaptic efficacy, depending on the relative timing of spikes and EPSPs. Besides these changes in the synaptic strength, recent reports indicate that intrinsic neuronal excitability can also be modified as a function of the postsynaptic activity. An increase in membrane excitability is induced in cultured cortical neurons by chronic blockade of synaptic activity (Desai *et al.* 1999) and in cerebellar neurons following high-frequency stimulation of their synaptic afferents (Aizenman & Linden, 2000; Armano *et al.* 2000). Furthermore, correlated pre- and postsynaptic activity can enhance presynaptic excitability, with concomitant modifications in EPSPs due to changes at the synapse itself (Ganguly *et al.* 2000).

In the present study, by means of *in vivo* intracellular recordings of striatal output neurons, we investigated the effect of a single action potential, naturally occurring on spontaneous synaptic depolarization, on subsequent EPSPs. This work was prompted by a previous study (Mahon *et al.* 2000*a*) showing that intrasomatic injection in striatal neurons of long lasting depolarizing current pulses, which led to repetitive discharge, induced a short-term increase in their membrane excitability. These GABAergic neurons, which provide the main input stage of the basal ganglia, receive monosynaptic glutamatergic inputs arising from the cerebral cortex (see Wilson, 1995*a*). Here, we show that timing spontaneous post-synaptic action potentials with stimulation of cortical afferents produces a time-dependent increase in the ability of cortically evoked EPSPs to induce firing. This increase in EPSP-spike coupling was not due to changes in the

synaptic strength but resulted from modifications in intrinsic electrical properties of the postsynaptic cell, which led to a lowering of the voltage firing threshold. The cellular mechanisms of this intrinsic plasticity were studied in cortico-striatal slices where a prior activation of striatal neurons induced an increase in their intrinsic excitability as well as in EPSP-spike coupling. Both phenomena were abolished during bath application of a low concentration of 4-aminopyridine (4-AP) indicating the involvement of a striatal voltage-dependent potassium current.

The possible implication of this new form of spike-dependent intrinsic plasticity in striatum-related associative learning is discussed.

METHODS

In vivo experiments

Animal preparation and surgery. Experiments were conducted *in vivo* on 22 adult male Sprague-Dawley rats (Charles River, France) weighing 220–300 g. Animals were initially anaesthetized with sodium pentobarbital (Sanofi, Libourne, France) (40 mg kg^{-1}, I.P.) and ketamine (Imalgène, Rhône Mérieux, France) (100 mg (kg body wt)$^{-1}$, I.M.). Heart rate and the electroencephalogram were continuously monitored to assess the depth of anaesthesia. Additional doses of pentobarbital (20 mg kg^{-1}, I.P.) were regularly administered to maintain low frequency (< 3 Hz) cortical waves. After initial anaesthesia, a cannula was inserted in the trachea and the animal was placed in a stereotaxic frame. Incision and pressure points were infiltrated with xylocaine 2 % (Astra, France) every 2 h. To obtain long-lasting stable intracellular recordings, rats were immobilized with gallamine triethiodide (Sigma, 40 mg I.M. every 2 h) and artificially ventilated. Body temperature was maintained at 36.5–37.5 °C with a homeothermic blanket (Harvard Apparatus Ltd, UK). At the end of the experiments, animals received an overdose of pentobarbital (200 mg kg^{-1}, I.P.). All experiments were performed in accordance with local Ethical Committee and EU guidelines (directive 86/609/EEC) and every precaution was taken to minimize stress and the number of animals used in each experiment.

Intracellular recordings and cell identification. Intracellular recordings of striatal output neurons ($n = 48$) were performed using glass micropipettes filled with 2 M potassium acetate (50–70 MΩ). Stereotaxic coordinates for striatal recordings were: 9.5 mm anterior to the interaural line, 3.5–4 mm lateral to the midline and 3.7–5.5 mm ventral to the cortical surface. This striatal sector corresponded to the projection field of the orofacial motor cortex (Deniau *et al.* 1996). Records were obtained in current clamp using an Axoclamp-2B amplifier (Axon Instruments, Union City, CA, USA). Recorded neurons were identified morphologically in some experiments in which neurobiotin (1.5 %, Vector Laboratories, Inc., Burlingame, CA, USA) was added to the pipette solution and intracellularly injected by passing positive current pulses (200 ms, 1 nA) for 5–10 min at the end of the recording session. Injected neurons were revealed using histochemical methods described previously (Charpier & Deniau, 1997). Labelled cells exhibited the typical morphological features of medium-sized spiny type I neurons, the main class of striatal output neuron (Chang *et al.* 1982). In addition, all recorded neurons displayed the distinctive electrophysiological characteristics of these cells (Nisenbaum *et al.* 1994; Nisenbaum & Wilson, 1995; Charpier *et al.* 1999; Mahon *et al.* 2000*a*): a resting membrane potential more negative than – 70 mV, a relatively low input resistance (42–74 MΩ) and a slow ramp-like depolarization, in response to a threshold current pulse, leading to a long latency of firing (see Fig. 6*Bc*). Resting membrane potential values were corrected according to the tip potential recorded extracellularly immediately after termination of the intracellular recording. The apparent input resistance was measured, at resting potential, from the membrane potential change at the end of hyperpolarizing or depolarizing current pulses ($n \geqslant 10$) of weak intensity (0.1–0.3 nA, 100 ms duration, every 1.55 s see Fig. 6*Aa* and *b*).

Control and spike-triggered stimulations (S-T). A bipolar steel electrode was inserted (1.5 mm depth) in the ipsilateral orofacial motor cortex (12.5 mm anterior to the interaural line, 3.8–4 mm lateral to the midline) to stimulate cortical afferents terminating in the striatum. Electrical stimulation (100 μs duration) evokes, in striatal cells, monosynaptic (latency 2–3 ms) glutamatergic EPSPs (Jiang & North, 1991; Kita, 1996; Charpier *et al.* 1999; Mahon *et al.* 2000*a*). In control condition, cortical stimuli were applied 80–150 times (every 1.55 s). Control firing probability (P_c), determined by the intensity of cortical stimulation, was calculated as the number of occasions that EPSPs evoked an action potential divided by the total number of trials. The spike-triggered protocols (S-T) consisted of triggering the cortical stimulation, at the same intensity as in control, after the occurrence of a spontaneous spike in the recorded striatal neuron. Intracellular action potentials, used to trigger the cortical stimulation, were detected with a voltage window discriminator (World Precision Instruments, CT, USA). The minimal temporal window to detect two successive spontaneous spikes was of 1.55 s. The number of S-T cortical stimuli was the same as in the control situation. The firing probability, in response to cortical stimulations, obtained during the S-T protocols ($P_{S\text{-}T}$) and its percentage of change relative to the control value $[(P_{S\text{-}T}/P_c) - 1] \times 100$, were quantified. Most striatal cells discharged spontaneously at rest with mean firing frequencies ranging from 0.1 to 0.9 Hz. In some cells (5 out of 24 neurons), with a particularly low firing rate, a small, positive DC current (0.1–0.3 nA) was injected to increase spontaneous activity.

Changes in intrinsic excitability during the S-T protocols were assessed by applying small hyperpolarizing (0.2–0.3 nA) and/or depolarizing (0.1–0.4 nA) current pulses first in isolation (every 1.55 s; 100 to 120 times), and then triggered by a prior (200 ms) spontaneous spike.

To determine the specific effect of the postsynaptic spike, cortical stimuli and current pulses were triggered after the detection of a subthreshold spontaneous EPSP (EPSP-T) or were applied 200 ms after an antidromic spike. Antidromic activation of striatal cells was achieved by electrical stimulation (100 μs duration) of the ipsilateral substantia nigra pars reticulata (Jaeger *et al.* 1994) (3.7 mm anterior to the interaural line, 2.4 mm lateral to the midline and 7.6–7.8 ventral to the cortical surface) using a bipolar concentric electrode (NE-100, Rhodes Medical Instruments, Woodland Hills, CA, USA).

Control responses, in which stimuli (cortical stimulations and current pulses) were preceded by a spontaneous spike in the recorded cell, were excluded from our analysis. We also discarded from both control and S-T protocols, trials in which evoked responses occurred simultaneously with spontaneous synaptic

depolarizations. In addition, during S-T protocols, trials where spontaneous spikes occurred between the detected spike and the test stimulation were discarded from the data base.

Data acquisition and analysis. Data were stored on-line with a Digital Tape Recorder (DRA-800, Biologic, Claix, France) and were then digitized with a sampling rate of 10 kHz for off-line analysis using Spike 2 software (Cambridge Electronic Design Ltd, UK). Statistical analysis and curve fitting were performed with Origin 6.0 (Microcal Software Inc., Northampton, MA, USA).

Action potential threshold was measured as the membrane potential at which the dV/dt exceeded 10 V s^{-1} (Fricker *et al.* 1999; see Fig. 2*A*). Action potential amplitude was calculated as the potential difference between the voltage threshold and the peak of the spike waveform. Rise time and total duration were measured from the threshold, to the peak of the spike and to the return to this voltage reference, respectively. The amplitude of subthreshold EPSPs was measured from the foot to the peak of the synaptic depolarization. The slope of depolarization of synaptically induced responses was determined by approximating the membrane depolarization, from the onset of the EPSP to the spike threshold for suprathreshold EPSPs, or to the peak of subthreshold EPSPs, as a straight line. *In vivo* and *in vitro* (see below) average data are reported as means ± S.E.M. unless stated otherwise. Statistical significance was assessed using Student's paired or unpaired t test (SigmaStat software). In some cases, non-parametric tests (Wilcoxon signed rank test or Mann-Whitney rank sum test) were used to supplement Student's t test.

***In vitro* experiments**

In vitro experiments were performed in parasagittal brain slices (400 μm thick) made from C57BL/6 mice aged 13–16 days. Slices were kept at room temperature in an oxygenated (95 % O_2–5 % CO_2) artificial CSF (ACSF) containing (mM): 125 NaCl, 2.5 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 1.25 NaH_2PO_4, 26 $NaHCO_3$, and 25 glucose, pH 7.4. Slices were transferred to a recording chamber where they were continuously perfused with oxygenated ACSF. Neurons were visualized throughout the experiment with an upright microscope using Normarski-type differential interference contrast optics combined with infrared videomicroscopy. Whole-cell current-clamp recordings of striatal neurons in the dorsal striatum were made at room temperature with patch electrodes pulled from borosilicate glass capillaries and filled with a solution containing (mM): 120 potassium gluconate, 20 KCl, 2 $MgCl_2$, 1 $CaCl_2$, 10 EGTA, 10 Hepes, and 2 Na_2-ATP, pH 7.3. Electrode resistance was 4–6 MΩ. Whole-cell membrane potentials were recorded with an EPC9 amplifier (Heka, Lambrecht, Germany) driven by a Macintosh Power PC. Recorded cells were visually and electrophysiologically identified as striatal output neurons (see above). Cells had a mean resting potential of –78.5 mV (±1.4 mV, n = 20 cells). EPSPs were evoked by electrical stimulation (100–150 μs duration) through a bipolar tungsten electrode placed at the cortex–striatum border in the presence of bicuculline (10 μM) throughout all the experiments. In some experiments, the potassium channels blocker 4-aminopyridine (4-AP, 100 μM) was added to the bath solution. In these experiments, a weak negative DC current (ranging between 10 and 60 pA) was injected to compensate for the small depolarization of the resting membrane potential induced by 4-AP. All drugs were applied in the perfusion solution. 4-AP and bicuculline were purchased from Fischer Bioblock Scientific (Illkirch, France). Data were acquired using 'Pulse' program (Heka) and analysed using macros written for Igor (Wavemetrix Inc., USA).

RESULTS

Spike-timing dependent increase in the probability to induce suprathreshold EPSPs

We examined, in intracellular records from striatal output neurons *in vivo*, how a spontaneous action potential affected subsequent monosynaptic responses evoked by stimulating cortical afferents. In the control conditions (Fig. 1*Aa*), cortical stimuli evoked suprathreshold responses in most cells (n = 21 out of 24) with a wide range of firing probabilities (from 0.02 to 0.93; mean 0.27 ± 0.04, n = 26 tests from 21 cells). In the three other neurons, control EPSPs were of large amplitude but did not, during the control period, initiate action potentials. In a first set of experiments, the spike-trigger procedure (S-T) consisted in stimulating cortical fibres 200 ms after the occurrence of a spontaneous postsynaptic spike (Fig. 1*Ab*). As shown by the S-T averaging of spontaneous intracellular activity (Fig. 1*Ab*, inset), this delay allowed the cell to recover its resting membrane potential. In all cases, including experiments where firing did not occur in control, the S-T protocol enhanced the probability that the cortically evoked EPSP initiated firing (P_c, 0.21 ± 0.03; $P_{S\text{-}T}$, 0.58 ± 0.04, n = 29 protocols, P < 0.0001, Student's paired t test; Fig. 1*Ac* and *d*). The mean increase in firing probability calculated from individual experiments was 345 ± 92 % (n = 26). This increased firing was not associated with a significant change of membrane potential as measured at the foot of the evoked EPSPs (Control, –75.2 ± 1 mV; S-T, –74.7 ± 1 mV, n = 24 cells, P > 0.3 for each cell, Student's unpaired t test).

We explored the time dependence of the S-T facilitation by testing different time intervals between the triggering spike and the cortical stimulation (Fig. 1*Ba*). In the cell illustrated in Fig. 1*Ba* and *b*, where the control firing probability was 0.55, the evoked firing was increased by 44.4 % at 200 ms. As the time interval was increased, the firing probability fell off exponentially with a time constant of 250 ms, recovering a control level at an interval of 800 ms (Fig. 1*Bb*). Pooling the data obtained from six striatal neurons (Fig. 1*Bc*), the average decay of the S-T facilitation had a time constant of 185 ms and recovery occurred at about 1 s.

Decrease in spike threshold and firing latency

To determine whether the increased firing on evoked synaptic potentials resulted from a change in the voltage firing threshold, we compared control threshold to that measured during the 200 ms S-T protocols. This analysis was applied in nine potentiated neurons, with a sufficient number of suprathreshold EPSPs (n > 8) in control to provide a reliable comparison with the conditioned responses. Spike thresholds were measured on individual cortically evoked suprathreshold EPSPs as shown in Fig. 2*A*. The superimposed records in Fig. 2*B* clearly show

that the S-T procedure reduced firing threshold. Analysis of pooled results ($n = 9$) revealed a significant decrease of the mean voltage threshold for spike initiation during the pairing protocol compared to the control situation (Control, –51.0 ± 0.6 mV; S-T, –52.5 ± 0.5 mV, $P < 0.001$, Student's paired t test; Fig. 2*C*). Similarly, the mean spike latency, measured from the onset of the evoked EPSPs (Fig. 2*A*), was significantly reduced by the S-T protocol (Control, 10.7 ± 1.6 ms; S-T, 9.2 ± 1.3 ms, $n = 9$, $P < 0.01$, Student's paired t test; Fig. 2*D*) with a mean decrease of 13.6 ± 3 %. As illustrated in Fig. 2*E*, we found that the change in spike threshold was correlated with an increase in the slope of the membrane depolarization preceding the action potential (Control, 2.80 ± 0.50 mV ms^{-1}; S-T, 3.09 ± 0.56 mV ms^{-1}, $n = 9$; $P < 0.01$, Student's paired t test). The amplitude, rise time and duration of action potentials obtained in control (mean, 61.1 ± 3.8 mV, 525 ± 30 μs and 1.53 ± 0.06 ms, respectively) were not modified by the S-T protocol ($P > 0.2$ for each parameter, Student's paired t test) suggesting that the kinetics and amplitude of voltage-gated currents associated with the spike itself were not affected.

We wished to test whether synaptic strength changed in parallel with this decrease in threshold of synaptically induced action potentials. The amplitude of subthreshold EPSPs was therefore measured in the nine neurons where the decrease in firing threshold was quantified. The amplitude of subthreshold EPSPs during S-T protocols did not significantly differ from that of respective controls ($P > 0.9$, Student's paired t test). Moreover, we did not detect any change in the slope of subthreshold EPSPs ($P > 0.3$, Student's paired t test).

Voltage window for the expression of the S-T facilitation

Our results show that a prior spontaneous action potential enhanced coupling between large near-threshold cortically evoked EPSPs and action-potential generation. We asked

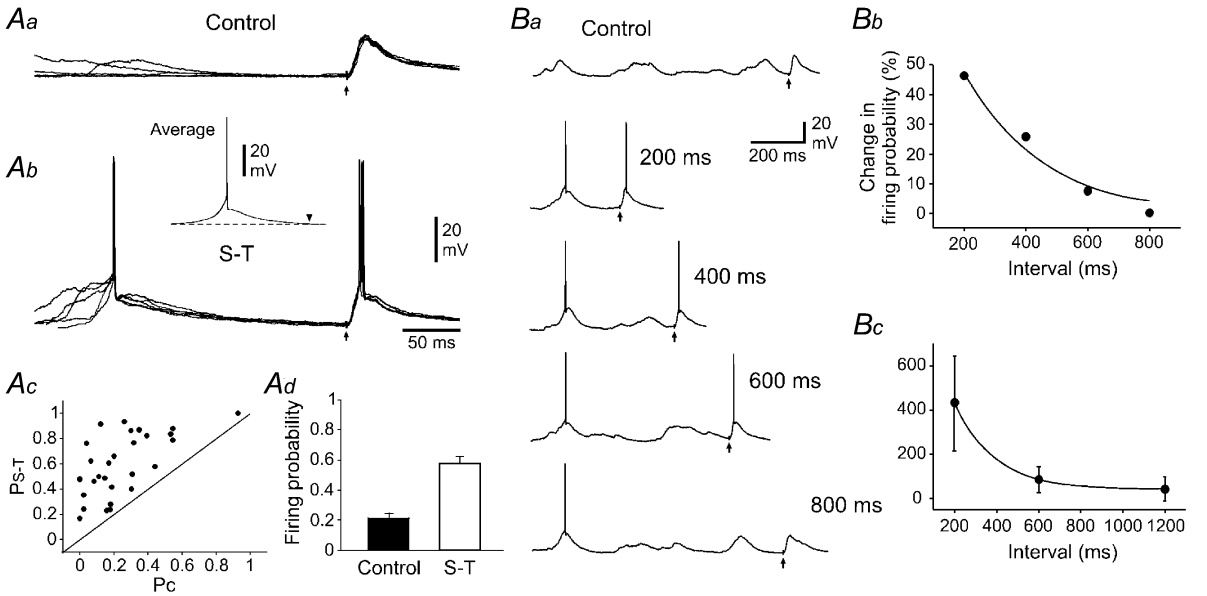

Figure 1. Short-term increase in the probability to induce a suprathreshold EPSP following a spontaneous action potential

Aa and *b*, superimposition of 5 successive cortically evoked responses in control (*Aa*) and during the 200 ms spike-trigger protocol (S-T, *Ab*). P_c, 0.04 ($n = 51$ trials); $P_{S\text{-}T}$, 0.76 ($n = 59$ trials). Here and in the following figures, filled arrows below records indicate the cortical stimulus artifact. *Ab* inset, from the same cell, spike-triggered averaging ($n = 40$) of spontaneous activity showed that 200 ms (arrowhead) after the triggering spikes the membrane potential recovered its resting value (dashed line, – 73 mV). *Ac*, relationship between the probability to induce suprathreshold cortically evoked EPSPs during the 200 ms S-T procedure ($P_{S\text{-}T}$) and the corresponding control probability (P_c) ($n = 29$ protocols from 24 neurons, $n = 15$ rats). In two cells, 4 and 3 separated protocols (using cortical stimulation of different intensities) were applied, respectively. The diagonal is the place where $P_{S\text{-}T}$ equals P_c. Note that all data points were above this line. *Ad*, summary histogram (from the 29 protocols shown in *Ac*) showing the robust increase in the mean firing probability ($P < 0.0001$, Student's paired t test) during the S-T synaptic stimulations. *Ba–c*, time window for the spike-triggered increase in firing probability. *Ba*, examples of cortically evoked responses in a striatal neuron during the control period and S-T protocols with progressively increasing time intervals. For each set of S-T protocols the corresponding control firing was the same. Triggering spikes are aligned. In this cell, the percentage increase in firing probability fell off exponentially as the time difference was increased, with a time constant of 250 ms ($r^2 = 0.96$; *Bb*). $n \geqslant 40$ trials for each series of time intervals. *Bc*, pooled data from six cells. The recovery of firing probability as a function of the time interval fitted with an exponential decay curve ($\tau = 185$ ms). Error bars are S.E.M.

whether spontaneous action potentials could also affect EPSP amplitude in experiments ($n = 9$ cells) where the 200 ms S-T protocol was tested with smaller amplitude EPSPs, which were induced by cortical stimuli of about 50 % of the threshold intensity. In control, the mean amplitude of these EPSPs was 8.2 ± 1.0 mV and they reached a peak potential of –66.1 ± 1.2 mV. As illustrated in Fig. 3*Aa* and *Ba*, the amplitude and kinetics of subthreshold EPSPs were not altered by the S-T procedure. The pooled data (Fig. 3*Ab*) show that the mean amplitude (7.6 ± 1.1 mV, $n = 9$) and peak potential (–66.6 ± 1.5 mV, $n = 9$) of EPSPs were not significantly modified ($P > 0.2$ for each parameter, Wilcoxon signed rank test) by the conditioning.

S-T facilitation could be restored by increasing the intensity of cortical stimulation so that some EPSPs elicited firing in control conditions (Fig. 3*Bb* and *c*). The summarized results (Fig. 3*Bc*) obtained from six neurons, in which S-T procedures were tested on small and large amplitude synaptic potentials, indicate that small EPSPs were not affected by the prior postsynaptic firing (Control, 6.8 ± 0.9 mV; S-T, 6.3 ± 0.9 mV, $P > 0.15$, Wilcoxon signed rank test) while in the same cells, the mean firing probability, calculated for strong stimuli, was increased by 205 ± 150 % ($P < 0.05$, Wilcoxon signed rank test).

The lack of changes in small EPSPs raises the question of how prior postsynaptic firing affects the synaptic input–output relationship. This was addressed in three cells, where 200 ms S-T protocols were tested with a wide range of cortical stimulation intensities. In the experiment shown in Fig. 4, the intensity of cortical stimulation was progressively increased, from subthreshold (2–5 V) to suprathreshold values (6 and 6.5 V). At each intensity, control and S-T procedures were successively applied (Fig. 4*A*) and EPSP amplitude and firing probability were measured. At all stimulus intensities, S-T protocols caused no change in the amplitude of subthreshold EPSPs ($P > 0.2$ for each intensity of stimulation, Student's unpaired *t* test; Fig. 4*B*, lower graph). However, when EPSPs approached the firing threshold (peak potential, −55 ± 0.7 mV, $n = 3$

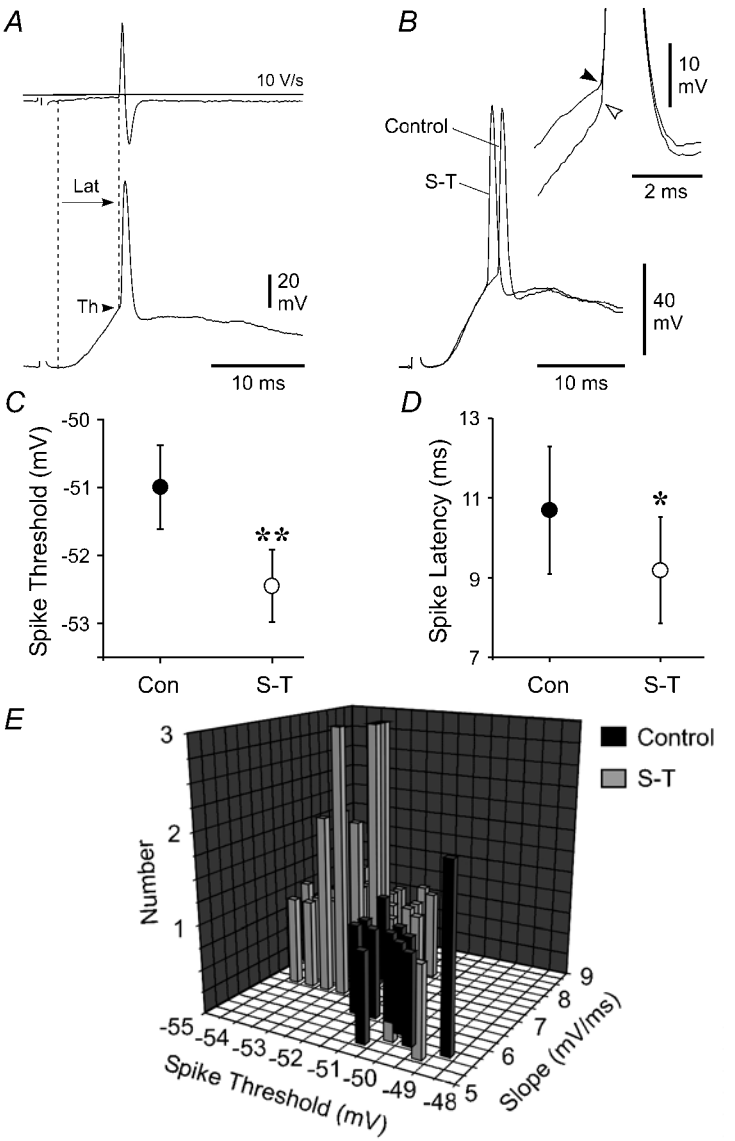

Figure 2. Cellular correlates of the increase in firing probability

A, measurement of the voltage firing threshold and spike latency in response to synaptic stimulation. The voltage threshold (lower trace, Th) was measured at the point corresponding to a $dV/dt \geqslant 10$ V s^{-1} (top trace, horizontal line). This threshold definition from the differentiated record was in agreement with the visual assessment. As indicated by the vertical dashed lines, spike latency (Lat) was measured as the time difference between the onset of the evoked EPSP and the spike threshold. *B*, examples of cortically induced responses obtained in control and during the 200 ms S-T protocol. Note the decrease in firing latency in the conditioned response (S-T) compared to the control. The DC superimposition of action potentials (inset) clearly shows a decrease in firing threshold of the spike-triggered response (right arrowhead) compared to the control (left arrowhead). Spikes are truncated. In the cell illustrated in *A* and *B*, P_c, 0.3 ($n = 40$ trials) and $P_{S\text{-}T}$, 0.86 ($n = 51$ trials). *C* and *D*, summary data from nine experiments showing that average values of spike threshold and spike latency were significantly decreased by the 200 ms S-T conditioning compared to the control condition (* $P < 0.01$; ** $P < 0.001$; Student's paired *t* test). For a reliable comparison of the parameters between the control and the S-T protocols, we used experiments where the number of control suprathreshold EPSPs was > 8. Error bars depict S.E.M. *E*, from a single cell, 3D bar graph showing the relationship between the spike threshold and the synaptic depolarization slope preceding the spike, in control (black bars) and during the 200 ms S-T protocol (grey bars). *A*, *B* and *C* are from the same experiment.

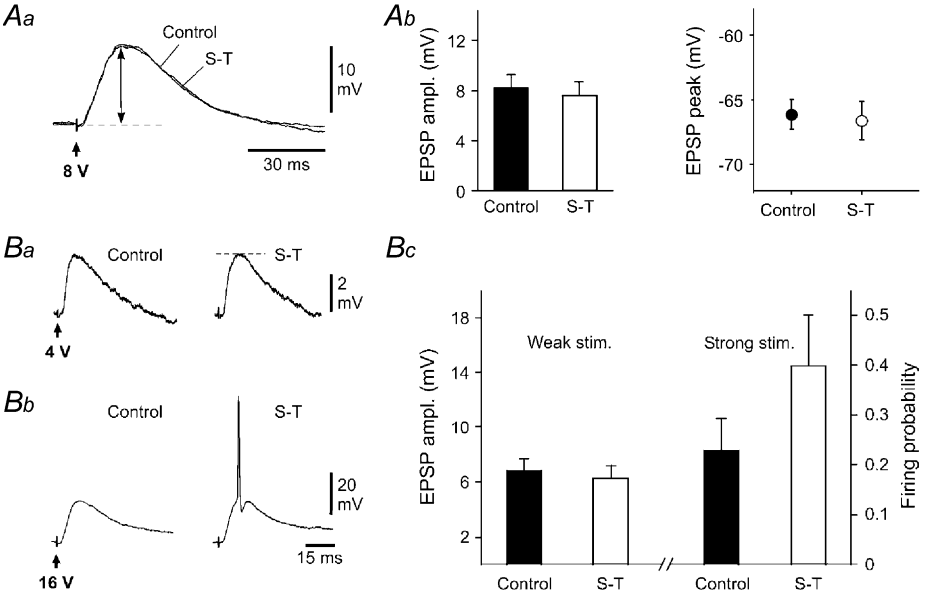

Figure 3. Small amplitude EPSPs are not affected by the S-T protocol

Aa, DC superimposition of averaged ($n = 6$) cortically evoked EPSPs in control and during the 200 ms S-T protocol. Amplitude of synaptic potential was measured as indicated, from the baseline (dashed line, –74 mV) to the peak of the synaptic depolarization. *Ab*, summary data from nine experiments showing that size and peak of small amplitude EPSPs are not significantly ($P > 0.2$, Wilcoxon signed rank test) modified by the S-T protocol. *Ba–c*, the S-T facilitation is restored by increasing the amplitude of evoked EPSPs. *Ba* and *b*, from a representative experiment, averaged (*Ba*, $n = 6$) and single (*Bb*) traces obtained in control and during the 200 ms S-T procedure. Small amplitude EPSPs evoked by weak cortical stimulation (*Ba*) showed no change, while a facilitation was observed (*Bb*) for a subsequent protocol with a strong cortical stimulus (P_c, 0.02, $n = 44$ trials; $P_{S\text{-}T}$, 0.24, $n = 33$ trials). *Bc*, summary bar graphs from six experiments where weak then strong cortical stimuli were applied. While EPSPs amplitude measured from weak stimuli was not altered by the S-T procedure ($P > 0.15$, Wilcoxon signed rank test), the firing probability calculated for strong stimuli was significantly increased ($P < 0.05$, Wilcoxon signed rank test). In *Aa*, *Ba* and *Bb* the intensity of cortical stimulation is indicated below the arrows. Error bars in *Aa* and *Bc* represent S.E.M.

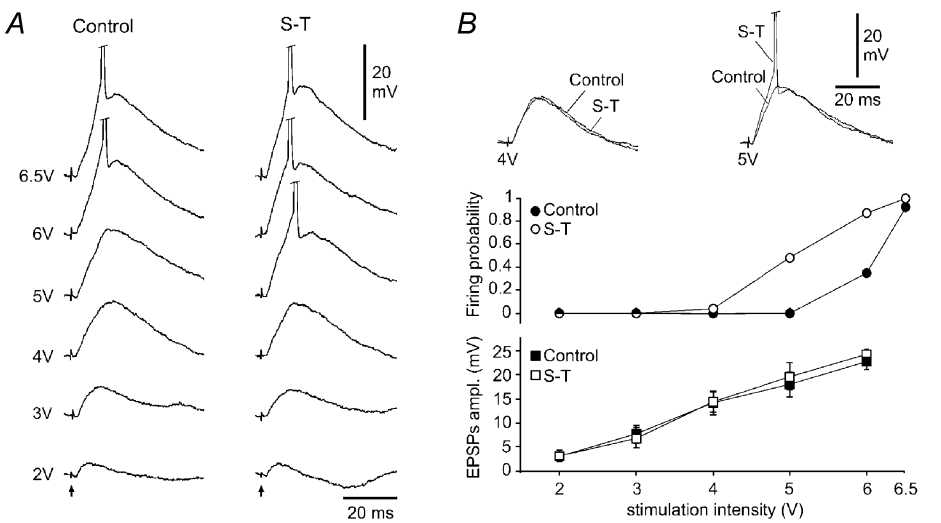

Figure 4. Effect of the S-T protocol on the cortico-striatal input–output relationship

A, records from a single neuron in response to cortical stimuli of increasing intensity (from bottom to top) in control situation (left) and during the corresponding 200 ms S-T protocol (right). Spikes are truncated. *B*, from the same cell as *A*, firing probability and amplitude of subthreshold EPSPs, in control and during S-T procedure, as a function of the cortical stimulation intensity. The top traces show the superimposition of control and S-T responses obtained for two different intensities of stimulation (same traces as *A*). The mean amplitude of EPSPs was measured from at least 20 trials. Error bars depict S.D.

cells), S-T protocols became effective and produced an increase in the firing probability (Fig. 4*B*, upper graph). Note that, at an intensity of 5 V, cortically evoked EPSPs never induced firing in control conditions but were quite efficient in eliciting postsynaptic discharges during the S-T procedure (Fig. 4*B*, right traces). This shows that the spike-dependent process decreases the threshold stimulation intensity, which corresponds to the minimal synaptic input that can generate a postsynaptic spike. Similar results were obtained in the two other cells.

Requirement of the postsynaptic spike

To understand how postsynaptic firing induces facilitation, we examined the effects of subthreshold spontaneous depolarizations on subsequent cortically evoked responses. In these experiments, cortical stimulations were triggered by a subthreshold spontaneous EPSP (EPSP-T) (Fig. 5*A*, middle traces). In the nine tested cells, the mean firing probability in control and during the EPSP-T procedure was 0.19 ± 0.06 and 0.32 ± 0.09, respectively, corresponding to weak facilitation ($n = 6$) or an absence of any effect ($n = 3$). In addition to inducing facilitation unreliably, subthreshold synaptic depolarizations had considerably less effect on firing probability. The percentage changes in firing probability were 64 ± 19 % ($n = 9$) for the EPSP-T protocol and 345 ± 92 % ($n = 26$) for the S-T procedure ($P < 0.05$, Mann-Whitney rank sum test; Fig. 5*C*). These experiments suggest that postsynaptic firing is required to induce a significant increase in firing probability. We confirmed this conclusion in two experiments where we successively applied control synaptic stimulations, a 200 ms EPSP-T protocol then a 200 ms S-T protocol. In the experiment illustrated in Figure 5*A*, the EPSP-T protocol produced a moderate increase in firing probability (P_c, 0.26; $P_{EPSP\text{-}T}$, 0.46, an increase of 77 %) while subsequent application of the S-T procedure led to a powerful facilitation ($P_{S\text{-}T}$, 0.93, an increase of 258 %). In the other neuron, while the subthreshold protocol had no effect, a subsequent S-T protocol induced a robust increase

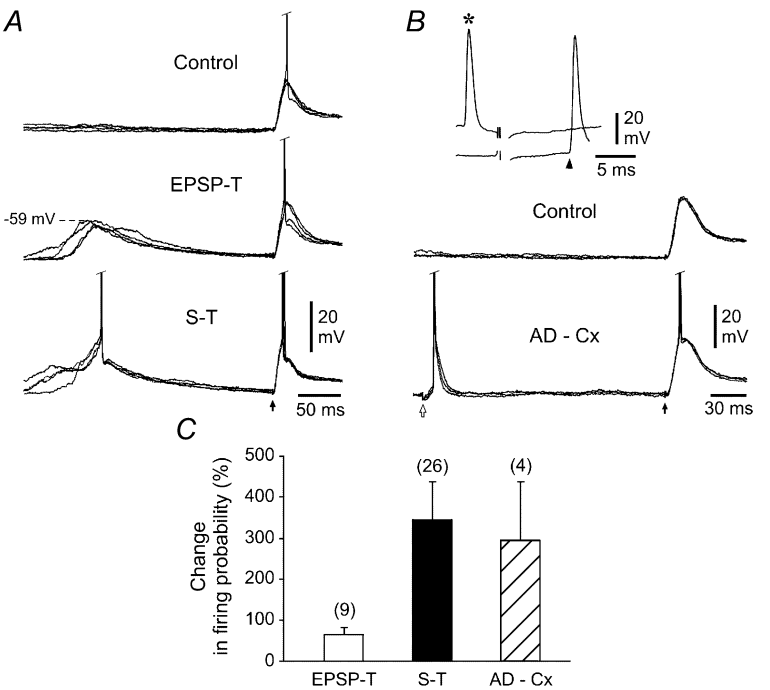

Figure 5. A postsynaptic spike is required for an increase in firing probability

A, spontaneous EPSPs alone do not induce a significant increase in firing probability. Superimposition of four successive responses in control (top) and during 200 ms EPSP-T (middle) and S-T (bottom) procedures. The probability of evoking firing in the different series of protocols was 0.26, 0.46 and 0.93, respectively. The dashed line indicates the peak potential of the triggering subthreshold EPSPs. *B*, preceding antidromic activation of striatal cells enhances the probability that cortically evoked EPSPs induce firing. From an individual experiment, superimposition ($n = 3$) of EPSPs evoked by cortical stimulation (Cx) obtained in control (top traces) and 200 ms after antidromic activation (open arrow; AD–Cx, bottom traces). The firing probabilities were 0.42 ($n = 69$) and 0.78 ($n = 59$ trials), corresponding to an increase of 85.7 % after antidromic firing. Inset, the lower trace shows the abrupt occurrence of the antidromic action potential from the resting potential (arrowhead) with no underlying synaptic depolarization. The upper record shows the collision of the antidromic spike with a spontaneous orthodromic action potential (*). *C*, group data allowing a comparison between changes in firing probability induced by EPSP-T, S-T protocols and AD–Cx pairings. The number of protocols is in parentheses. Error bars depict S.E.M. In *A* and *B*, spikes are truncated.

in firing probability (P_c, 0.04; P_{EPSP-T}, 0.03; P_{S-T}, 0.76; same cell as in Fig. 1*Aa* and *b*).

To test whether striatal cell firing alone could facilitate EPSP-spike coupling, the effects of an antidromic spike (AD spike) on subsequent synaptic potentials were examined ($n = 4$ cells). In this way we could study the effects of an action potential without additional synaptic or current-induced depolarization. Antidromic activation (AD latencies ranged from 8.1 to 11.1 ms) of striatal output neurons was achieved by stimulating the substantia nigra pars reticulata. AD spikes were defined by their all or none behaviour and by collision tests with an orthodromic spike (Fig. 5*B*, inset). The pairing protocol consisted in applying the cortical stimuli 200 ms after the AD spike was evoked. As illustrated in Fig. 5*B*, prior AD activation also increased the ability of cortical stimulation to evoke suprathreshold responses. In the four tested cells, the mean control firing probability was 0.27 ± 0.08 and reached 0.75 ± 0.06 when an AD spike preceded synaptic stimulations. This increase in firing probability (295 ± 142 %) induced by an AD spike was similar ($P > 0.6$, Mann-Whitney rank sum test) to that calculated from S-T protocols and was significantly higher ($P < 0.05$, Student's unpaired *t* test) than that induced by subthreshold EPSPs (Fig. 5*C*).

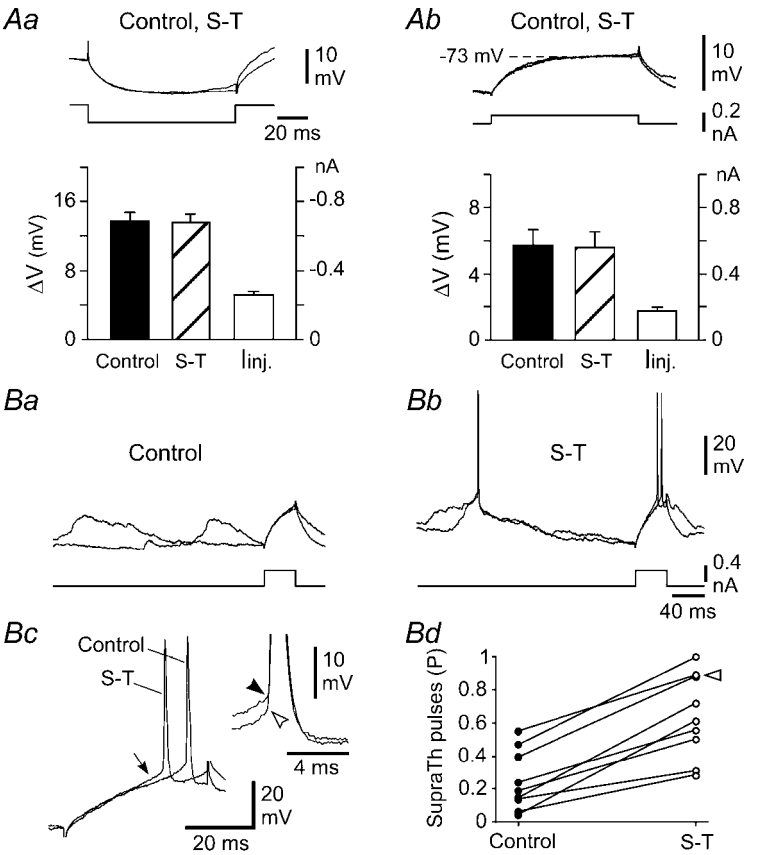

Figure 6. Spike-triggered increase in intrinsic excitability

Aa and *b*, preceding action potentials do not modify apparent input resistance. Summary data showing the mean voltage changes (ΔV) in striatal neurons in response to intracellular injection of negative (*Aa*; $n = 7$ cells) and positive current pulses (*Ab; n* = 4 cells) of weak intensity (I_{inj}) in control and during 200 ms S-T protocols. The DC superimposition of averaged ($n = 10$) records (top traces) from an individual cell shows that the current-induced responses did not change indicating that the S-T protocol did not modify input resistance, measured in either the hyperpolarizing (*Aa*) or depolarizing (*Ab*) directions. The level of steady membrane potential reached during the depolarizing current is indicated by the dashed line in *Ab*. *Ba–d*, the S-T protocol increases the reliability of threshold current pulses to induce firing. *Ba and b*, superimposition of two successive voltage responses induced by direct injection of threshold current pulses in control situation (*Ba*) and triggered (200 ms interval) by spontaneous firing (*Bb*). *Bc*, superimposition of supra-threshold responses obtained in control and during the S-T protocol. Note the decrease in firing latency, measured from the onset of the current pulse to the threshold of the spike, in the conditioned response. The DC superimposition of the spikes (inset) shows the reduction in spike threshold in the S-T procedure (right arrowhead) compared to the control situation (left arrowhead). Spikes are truncated. *Bd*, group data (nine individual cells) showing the relation between the probability that threshold current pulses induces firing in control and during the S-T protocols. The arrowhead indicates the experiment shown in *Ba–c*.

Spike-dependent increase in intrinsic excitability

The spike-dependent increase in EPSP-spike coupling was not associated with a detectable change in EPSP amplitude. Therefore, we performed a number of experiments to assess possible changes in intrinsic excitability that could account for the increase in cell responsiveness.

First, voltage responses to small isolated current pulses were compared to those triggered 200 ms after a spontaneous action potential. The mean voltage changes induced by hyperpolarizing (Fig. 6*Aa*, $n = 7$ cells) and subthreshold depolarizing (Fig. 6*Ab*, $n = 4$ cells) current pulses were not altered by the S-T protocol ($P > 0.5$, Student's paired t test). This lack of change in the apparent input resistance indicates that prior spontaneous spiking did not modify voltage-dependent conductances close to the resting potential of striatal neurons (see Nisenbaum & Wilson, 1995). Similar results were obtained at comparable intervals after an AD action potential (not shown). It is important to stress that these results are consistent with the relative stability of subthreshold EPSPs since changes in dendritic or somatic input resistance should modify the amplitude and shape of propagated dendritic EPSPs recorded from the soma (Wilson, 1995*b*).

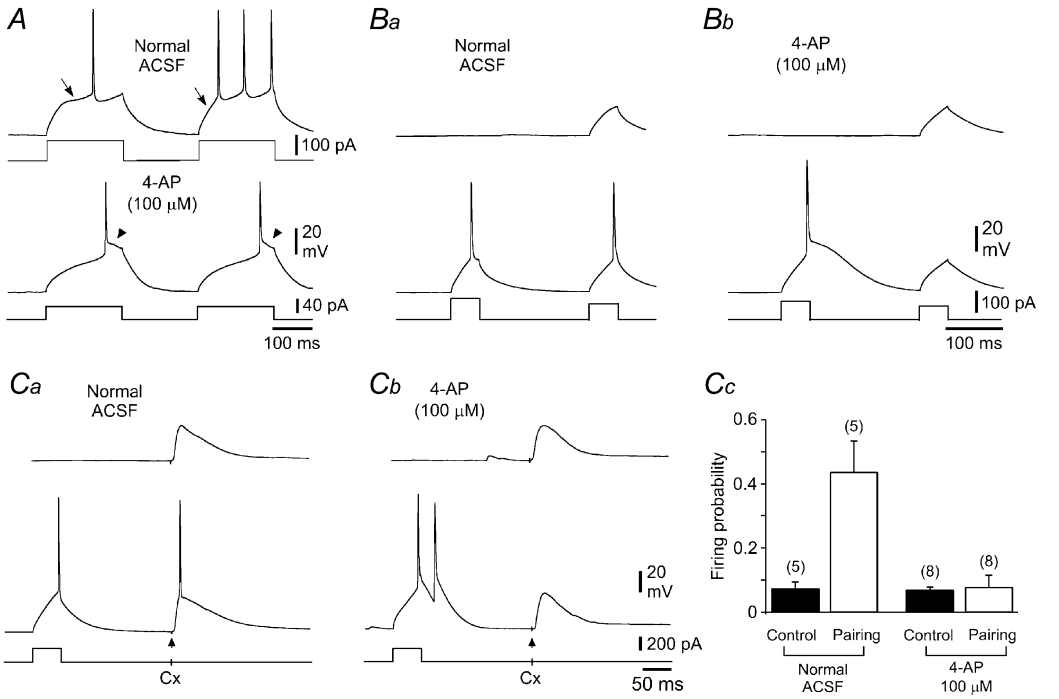

Figure 7. Effect of 4-AP on the activity-dependent increase in striatal neurons excitability *in vitro*

A, voltage responses of a striatal neuron to injection of two successive identical current pulses in normal ACSF (top trace) and when the cell was exposed to extracellular 4-AP (100 μM; bottom trace). In normal medium, the increase in the responsiveness of the neuron was associated with a marked increase in the slope depolarization preceding the firing (arrows). The increase in membrane excitability was absent in the presence of 4-AP. Note the post-spike depolarization due to the potassium channels blocker (arrowheads). *Ba* and *b*, effect of a prior direct activation on current-induced subthreshold depolarizations in normal medium (*Ba*) and after exposure to 4-AP (*Bb*). In control (top traces), test current pulses induced membrane depolarization just below spike threshold. Before drug application (*Ba*), when preceded by a suprathreshold direct stimulation, subthreshold currents became efficient to generate spike discharges (bottom trace, firing probability 1, $n = 50$ trials). In the same cell, when 4-AP was present in the bath solution, this pairing protocol was without effect on the subthreshold test responses. *Ca–c*, the use-dependent increase in EPSP-spike coupling is abolished by 4-AP. *Ca and b*, in control (top traces), cortically evoked EPSPs were obtained in isolation. During the pairing protocols (bottom traces), synaptic stimulations were applied 200 ms after the onset of a suprathreshold current pulse. In normal medium (*Ca*), this conditioning produced a robust increase in the probability to evoke suprathreshold EPSPs ($P_{control}$, 0.09; $P_{pairing}$, 0.24, $n = 100$ trials in each condition) while it had no significant effect when 4-AP was added in the extracellular solution ($P_{control}$, 0.07; $P_{pairing}$, 0.12, $n = 100$ trials in each condition). *Cc*, pooled data showing the robust use-dependent increase in firing probability on EPSPs in normal condition ($P < 0.02$, Student's paired t test) and the lack of facilitation in presence of the potassium channels blocker ($P > 0.9$, Student's paired t test). In two cells (including the neuron shown in *Ca* and *b*), control and paired stimulations were applied in the normal and poisoned medium. Current pulses and the time of cortical stimulation are indicated below the voltage responses. Resting membrane potentials were −83 mV (*A*), −78 mV (*Ba* and *b*) and −80 mV (*Ca* and *b*).

In another set of experiments we asked whether membrane excitability was enhanced at potentials close to the firing threshold. Responses to threshold depolarizing current pulses in control conditions (Fig. 6*Ba*) were compared to those obtained 200 ms after a spontaneous postsynaptic spike (Fig. 6*Bb*). In all tested cells (Fig. 6*Bd*), the probability that current injections induced firing was markedly enhanced (P_c, 0.25 ± 0.06; $P_{S\text{-}T}$, 0.64 ± 0.09; $n = 9$ cells, $P < 0.0001$, Student's paired *t* test), with a mean increase of 309 ± 133 %. We further characterized the increase in excitability on threshold current pulses by measuring the changes in spike latency and spike threshold in six cells, in which the number of control suprathreshold responses was sufficient for a reliable comparison. As observed for synaptic responses, the change in excitability was associated with both a decrease in the spike latency (–22.8 ± 7 %, $n = 6$ cells; see Fig. 6*Bc*) and a reduction of the voltage threshold for action potentials (control, –47.4 ± 0.3 mV; S-T, –48.4 ± 0.2 mV, $n = 6$, $P < 0.01$, Student's paired *t* test; Fig. 6*Bc*, inset). In addition, similarly to the conditioned EPSPs, the slope of membrane depolarization was steeper during the S-T protocols (Fig. 6*Bc*, arrow). The AD spike was also effective in increasing the firing probability on current-induced responses, giving a 100 % of increase in the two cells tested. The increase in cell firing on threshold current pulses was not present any more when the spontaneous spike preceded the current pulses by 1 s ($n = 2$ cells).

These results demonstrate that a single action potential enhances cellular excitability by increasing the reliability with which a threshold current induces firing but without modifying voltage changes in response to subthreshold currents.

The increase in excitability is abolished *in vitro* by low concentration of 4-AP

Our *in vivo* data indicate that the spike-dependent increase in EPSP-spike coupling is associated with a change in membrane excitability at potentials close to the firing threshold. This change in cell responsiveness was associated with an increase in the slope of membrane depolarization preceding cell firing and a lowering of voltage spike threshold. This could be the result of an activity-dependent inactivation of an outward slowly inactivating potassium A-current (I_{As}), which is responsible in striatal cells for slowing the rate of membrane depolarization from potentials near –60 mV (Nisenbaum *et al.* 1994; Gabel & Nisenbaum, 1998). To test this hypothesis we performed whole cell, patch-clamp recordings from striatal output neurons in a slice preparation of dorsal striatum and examined the effect of a specific blockade of I_{As} on the activity-dependent increase in striatal neurons excitability.

We first tested for changes in membrane excitability using repeated current injections (Fig. 7*A*, B*a* and *b*). In normal medium, application of two successive (time interval of 200 ms) suprathreshold current pulses, of same intensity and duration, resulted in an increase of the number of action potentials evoked by the second current pulse injection (conditioning pulses, 1.12 ± 0.11 spikes; test pulses, 2.57 ± 0.29 spikes, $P < 0.04$, Student's paired *t* test, $n = 3$ cells; Fig. 7*A*, top trace). This facilitation was associated with a marked increase in the slope depolarization preceding the first action potential (Fig. 7*A*, top trace, arrows). In the same group of cells , extracellular application of a low concentration of 4-AP (100 μM), known to specifically block I_{As} in striatal neurons (Surmeier *et al.* 1991; Nisenbaum *et al.* 1994; Nisenbaum & Wilson, 1995), abolished the increase in cell responsiveness (Fig. 7*A*, bottom trace) (conditioning pulses, 1.13 ± 0.8 spikes; test pulses, 1.03 ± 0.13 spikes, $P > 0.15$, Student's paired *t* test, $n = 3$ cells). In another set of experiments, we found that subthreshold current pulses (Fig. 7*Ba*, top trace) were converted into suprathreshold current pulses when preceded by a short (50 ms duration) current pulse evoking a single action potential (Fig. 7*Ba*, bottom trace) (firing probability of 0.74 ± 0.13, 50 trials, $n = 6$ cells). Again, this facilitation was completely suppressed when 4-AP (100 μM) was added to the bath solution (Fig. 7*Bb*).

We further addressed the impact of direct suprathreshold stimulations on subsequent EPSPs evoked by electrical stimulation of cortical fibres ($n = 11$ cells). In control situations, synaptic stimulations were applied in isolation (every 5 s and the conditioning procedures consisted of delivering cortical stimuli 200 ms after a short (50 ms duration) suprathreshold current pulse ($n = 100$ trials for control and paired stimulations). In normal medium ($n = 5$ cells; Fig. 7*Ca*), the mean probability of inducing suprathreshold synaptic responses was of 0.07 (±0.02) in control and reached 0.44 (±0.1) during the pairing protocol, corresponding to a mean increase of 847.8 % ($P < 0.02$, Student's paired *t* test; Fig. 7*Cc*). Similarly to that observed *in vivo*, this increase in firing probability was not due to a change in the synaptic strength as indicated by the constancy in amplitude of subthreshold EPSPs (control, 24.4 ± 2.5 mV; pairing, 24.8 ± 2.6 mV, $P > 0.15$, Student's paired *t* test). Following bath application of 4-AP (100 μM; $n = 8$ cells; Fig. 7*Cb*), the firing probabilities on cortically evoked EPSPs, in control and during the pairing protocols, were found to be similar ($P_{control}$, 0.068 ± 0.01; $P_{pairing}$, 0.070 ± 0.04, $P > 0.9$, Student's paired *t* test; Fig. 7*Cc*) and subthreshold EPSPs remained unchanged (control, 23 ± 2.1 mV; pairing, 23 ± 2.5 mV; $P > 0.9$, Student's paired *t* test).

DISCUSSION

Our *in vivo* data indicate that a single action potential in striatal cells induces a short-term increase in the ability with which cortico-striatal EPSPs induce firing with no detectable increase in EPSP amplitude. This spike-

dependent facilitation was associated with a change in membrane excitability resulting in a lowering of the voltage firing threshold. Since this intrinsic plasticity was induced by a spontaneously occurring action potential, it would provide a natural process by which a single cell regulates, according to its recent firing history, the reliability of spike generation during afferent synaptic activation.

Lack of synaptic changes

The enhancement of EPSP-spike coupling might result from processes which augment excitatory synaptic efficacy. First, a proportion of the cortical afferents, contributing to the generation of the spontaneous postsynaptic spike used as the trigger event, might potentially be reactivated by the S-T cortical stimulation. This repeated activation of excitatory afferents could cause a short-term presynaptic facilitation as observed during paired-pulse stimulation (Fisher *et al.* 1997). Second, spontaneous synchronous firing of cortical cells, which normally initiates firing of striatal neurons (Wilson, 1995*a*; Mahon *et al.* 2001), could be followed by a rebound in cortical excitability. The cortical stimulus during the S-T procedure could then recruit additional cortico-striatal afferents and so increase the evoked postsynaptic response. However, both these processes would be expected to increase the amplitude of subthreshold EPSPs, and such increases were not detected in the present experiments. In addition, the S-T averaging of spontaneous activity (see Fig. 1*Ab*, inset) did not reveal a rebound of synaptic depolarization at the time where the facilitation was observed.

Alternatively, this facilitation might result from a reduction in the strength of inhibitory control following postsynaptic firing. Such a process has been described *in vitro* in hippocampal pyramidal cells where GABAergic inhibition is dramatically decreased following a postsynaptic train of action potentials (Pitler & Alger, 1992). However, a depression of GABAergic inputs, which terminate on the soma and proximal dendrites of striatal cells (Kita, 1993), should attenuate the inhibitory shunt of glutamatergic EPSPs propagating from distal dendritic spines (Dubé *et al.* 1988) and so increase their amplitude. Furthermore, we detected no increase in the somatic input resistance of striatal cells during the 200 ms S-T protocol, which is inconsistent with a reduced inhibitory synaptic conductance.

Intrinsic mechanisms

The most straightforward explanation for the observed facilitation is a use-dependent increase in intrinsic cellular excitability in a voltage window close to the firing threshold. This hypothesis is supported by the observation that S-T protocols did not modify small amplitude EPSPs (see above) and that only postsynaptic responses, close to or above spike threshold, were reinforced. Moreover, the S-T protocol enhanced the ability of threshold current pulses to trigger action potentials without affecting the membrane input resistance measured either in the depolarizing or hyperpolarizing direction close to resting potential.

The increase in probability that EPSPs induced firing was correlated with a decrease in the membrane depolarization required for spike generation. This decrease in spike threshold was associated with an increase in the mean rising slope of the evoked EPSPs. Voltage firing threshold is defined as the potential where the summed inward current exceeds the outward current (Noble & Stein, 1966). However, the kinetic properties of voltage-dependent Na^+ and K^+ conductances involved in action potential generation (Hodgkin & Huxley, 1952) suggest that the spike threshold depends critically on the rate of membrane depolarization (see for review Azouz & Gray, 2000; but also Fricker *et al.* 1999). Specifically, the fast inactivation of Na^+ channels is expected to confer an inverse relationship between the spike threshold and the prior slope of membrane depolarization (Holden & Yoda, 1981). This has been observed *in vivo* in neocortical neurons (Azouz & Gray, 2000), in hippocampal cells (Henze & Buzsáki, 2001) and in striatal output neurons (Wickens & Wilson, 1998).

In our *in vitro* experiments, a direct activation of striatal neurons induced an increase in cell firing on subsequent current- or synaptically induced depolarizations, as observed *in vivo*. The induction of this facilitation was blocked by a low concentration of 4-AP. This pharmacological manipulation of striatal neurons is known to specifically affect I_{As}, a voltage-dependent slowly inactivating potassium A-current that controls the cell firing by slowing the rate of membrane depolarization from about -60 mV (Nisenbaum *et al.* 1994; Nisenbaum & Wilson, 1995; Gabel & Nisenbaum, 1998; see also Figs 6*Bc* and 7*A*). It is noteworthy that in other central neurons, exhibiting a voltage-dependent potassium current similar to the striatal I_{As}, an increase in intrinsic membrane excitability has been previously described *in vitro* during repetitive membrane depolarization (Storm, 1988; Turrigiano *et al.* 1996). Here, a use-dependent inactivation of I_{As} following a spontaneous action potential could therefore account for the observed acceleration of cortically evoked synaptic potentials and consequently for the reduction of the voltage spike threshold. This hypothesis is also supported by a recent computer model (Mahon *et al.* 2000*b*) showing that an increase in striatal neurons excitability following direct stimulations could originate in the slow kinetics of I_{As}.

The causal relationship between the rate of depolarization and spike threshold depends on the assumption that our presumably somatic recordings reliably reflect voltage changes at the site of spike initiation. If action potentials in

striatal neurons are initiated, as in many central neurons, at the axon initial segment or the first node of Ranvier (Coombs *et al.* 1957; Stuart & Häusser, 1994; Colbert & Johnston, 1996), and the electrotonic length of these structures is short (Gogan *et al.* 1983; Colbert & Johnston, 1996), then voltage fluctuations at the spike initiation site should be similar to those recorded at the soma.

Such a use-dependent decrease in spike threshold by modulation of intrinsic conductances has already been described. In cortical neurons maintained in culture, Desai *et al.* (1999) showed that a long-lasting deprivation of evoked synaptic activity decreased the voltage firing threshold, due to a modification in the balance between inward and outward voltage-dependent currents. Moreover, a lowering in presynaptic firing threshold in hippocampal neurons, after repetitive correlated activity of pre- and postsynaptic cells, results from changes in gating kinetics of presynaptic Na^+ channels (Ganguly *et al.* 2000).

A new form of spike-dependent plasticity

The Hebbian theory postulated that synaptic strength could be changed by correlated pre- and postsynaptic activity. It is now widely assumed that a postsynaptic action potential, via its back-propagation to dendrites, provides the necessary associative signal (for review see Markram *et al.* 1997; Linden, 1999 and Bi & Poo, 2001). The short-term plasticity described here provides a new spike-dependent mechanism whereby the functional efficacy of incoming synaptic inputs, i.e. their ability to generate a postsynaptic spike, is reinforced. Although this process requires postsynaptic firing, its conditions of induction and properties of expression differ from those of the 'classical' spike-dependent synaptic plasticity. Here, the increase in firing probability is not associated with a change in synaptic strength but results from an increase in membrane excitability. In addition, it is induced by a single action potential rather than repetitive coupling of synaptic activity and postsynaptic spike. This process is of shorter duration than long-term spike-dependent synaptic plasticity, with a decay time course rather similar to that of synaptic facilitation (Fisher *et al.* 1997). The intrinsic plasticity described here could be induced *in vivo* following an antidromic activation or *in vitro* by an intrasomatic injection of a threshold current pulse indicating that its induction was not related to a specific set of excitatory synaptic inputs. Therefore, the striatal firing, whatever its synaptic origin, could affect the cellular excitability and enhance the functional impact of converging inputs that could include cortico-striatal fibres which were not involved in the prior postsynaptic firing.

Possible implications in striatal functions

The synaptically induced firing which we used as a conditioning stimulus results from synchronous discharges of many cortico-striatal neurons (Wilson, 1995*a*; Mahon *et al.* 2001). Cortico-striatal projections are organized topographically, with different striatal sectors processing information from distinct cortical regions (for review see Deniau *et al.* 1996). However, functionally associated cortical areas, such as motor and somatosensory cortices, terminate on overlapping zones within the striatum (Flaherty & Graybiel, 1993; Deniau *et al.* 1996). The spike-dependent increase in excitability establishes a short temporal window, in which the striatal output neuron becomes more responsive to subsequent excitatory synaptic inputs. This process could provide a temporal link to optimize striatal cell firing during temporally ordered activity of converging cortical inputs, normally associated during the completion of a given task.

This temporal association between cortical information within the striatum could provide a cellular mechanism underlying the role of the striatum in procedural learning leading to acquisition of habits (Graybiel, 1995). During learning of a sensory-motor association, the sensory cue becomes effective to discharge the related striatal neurons. The spike-dependent intrinsic plasticity could favour the integration in the striatum of subsequent sensory and motor information required for the correct execution of the behavioural task, cortical information that would remain ineffective if presented in isolation. Therefore, repeated association during training would lead to repetitive discharges in the selected striatal cells, a post-synaptic activity required for the induction of long-term potentiation at active cortico-striatal synapses (Charpier & Deniau, 1997; Charpier *et al.* 1999). Thus, the short-term increase in intrinsic excitability and the subsequent induction of long-term synaptic potentiation would durably reinforce the efficiency of associated cortico-striatal inputs, leading to stabilization of striatal sensory-motor engrams and consequently to acquisition of behavioural routines.

REFERENCES

Aizenman CD & Linden DJ (2000). Rapid, synaptically driven increases in the intrinsic excitability of cerebellar deep nuclear neurons. *Nat Neurosci* **3**, 109–111.

Armano S, Rossi P, Taglietti V & D'Angelo E (2000). Long-term potentiation of intrinsic excitability at the mossy fiber-granule cell synapse of rat cerebellum. *J Neurosci* **20**, 5208–5216.

Azouz R & Gray CM (2000). Dynamic spike threshold reveals a mechanism for synaptic coincidence detection in cortical neurons *in vivo*. *Proc Natl Acad Sci U S A* **97**, 8110–8115.

Bi GQ & Poo MM (2001). Synaptic modification by correlated activity: Hebb's postulate revisited. *Annu Rev Neurosci* **24**, 139–166.

Chang HT, Wilson CJ & Kitai ST (1982). A Golgi study of rat neostriatal neurons: light microscopic analysis. *J Comp Neurol* **208**, 107–126.

Charpier S & Deniau J-M (1997). *In vivo* activity-dependent plasticity at cortico-striatal connections: evidence for physiological long-term potentiation. *Proc Natl Acad Sci U S A* **94**, 7036–7040.

Charpier S, Mahon S & Deniau J-M (1999). *In vivo* induction of striatal long-term potentiation by low-frequency stimulation of the cerebral cortex. *Neuroscience* **91**, 1209–1222.

Colbert CM & Johnston D (1996). Axonal action-potential initiation and Na^+ channel densities in the soma and axon initial segment of subicular pyramidal neurons. *J Neurosci* **16**, 6676–6686.

Coombs JS, Curtis DR & Eccles JC (1957). The interpretation of spike potentials in motoneurons. *J Physiol* **139**, 198–231.

Deniau J-M, Menetrey A & Charpier S (1996). The lamellar organization of the rat substantia nigra pars reticulata: segregated patterns of striatal afferents and relationship to the topography of corticostriatal projections. *Neuroscience* **73**, 761–781.

Desai NS, Rutherford LC & Turrigiano GG (1999). Plasticity in the intrinsic excitability of cortical pyramidal neurons. *Nat Neurosci* **2**, 515–520.

Dubé L, Smith AD & Bolam JP (1988). Identification of synaptic terminals of thalamic or cortical origin in contact with distinct medium-size spiny neurons in the rat neostriatum. *J Comp Neurol* **267**, 455–471.

Fisher SA, Fischer TM & Carew TJ (1997). Multiple overlapping processes underlying short-term synaptic enhancement. *Trends Neurosci* **20**, 170–177.

Flaherty AW & Graybiel AM (1993). Tow input systems for body representations in the primate striatal matrix: experimental evidence in the squirrel monkey. *J Neurosci* **13**, 1120–1137.

Fricker D, Verhungen JA & Miles R (1999). Cell-attached measurements of the firing threshold of rat hippocampal neurones. *J Physiol* **517**, 791–804.

Gabel LA & Nisenbaum ES (1998). Biophysical characterization and functional consequences of a slowly inactivating potassium current in neostriatal neurons. *J Neurophysiol* **79**, 1989–2002.

Ganguly K, Kiss L & Poo MM (2000). Enhancement of presynaptic neuronal excitability by correlated presynaptic and postsynaptic spiking. *Nat Neurosci* **3**, 1018–1026.

Gogan P, Gueritaud JP & Tyc-Dumont S (1983). Comparison of antidromic and orthodromic actions potentials of identified motor axons in the cat's brain stem. *J Physiol* **335**, 205–220.

Graybiel AM (1995). Building action repertoires: memory and learning functions of the basal ganglia. *Curr Opin Neurobiol* **5**, 733–741.

Henze DA & Buzsaki G (2001). Action potential threshold of hippocampal pyramidal cells *in vivo* is increased by recent spiking activity. *Neuroscience* **105**, 121–130.

Holden AV & Yoda M (1981). The effects of ionic channel density on neuronal function. *J Theor Neurobiol* **1**, 60–81.

Hodgkin AL & Huxley AF (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol* **117**, 500–544.

Jaeger D, Kita H & Wilson CJ (1994). Surround inhibition among projection neurons is weak or nonexistent in the rat neostriatum. *J Neurophysiol* **72**, 2555–2558.

Jiang ZG & North RA (1991). Membrane properties and synaptic responses of rat striatal neurones *in vitro*. *J Physiol* **443**, 533–553.

Kita H (1993). GABAergic circuits of the striatum. *Prog Brain Res* **99**, 51–72.

Kita H (1996). Glutamatergic and GABAergic postsynaptic responses of striatal spiny neurons to intrastriatal and cortical stimulation recorded in slice preparations. *Neuroscience* **70**, 925–940.

Linden DJ (1999). The return of the spike: postsynaptic action potentials and the induction of LTP and LTD. *Neuron* **22**, 661–666.

Mahon S, Delord B, Deniau J-M & Charpier S (2000*a*). Intrinsic properties of rat striatal output neurones and time-dependent facilitation of cortical inputs *in vivo*. *J Physiol* **527**, 345–354.

Mahon S, Deniau J-M & Charpier S (2001). Relationship between EEG potentials and intracellular activity of striatal and cortico-striatal neurons: an *in vivo* study under different anesthetics. *Cereb Cortex* **11**, 360–373.

Mahon S, Deniau J-M, Charpier S & Delord B (2000*b*). Role of a striatal slowly inactivating potassium current in short-term facilitation of corticostriatal inputs: a computer simulation study. *Learn Mem* **7**, 357–362.

Markram H, Lubke J, Frotscher M & Sakmann B (1997). Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science* **275**, 213–215.

Nisenbaum ES & Wilson CJ (1995). Potassium current responsible for inward and outward rectification in rat neostriatal spiny projection neurons. *J Neurosci* **15**, 4449–4463.

Nisenbaum ES, Xu ZC & Wilson CJ (1994). Contribution of a slowly inactivating potassium current to the transition to firing of neostriatal spiny projections neurons. *J Neurophysiol* **71**, 1174–1189.

Noble D & Stein RB (1966). The threshold for initiation of action potentials by excitable cells. *J Physiol* **187**, 129–162.

Pitler TA & Alger BE (1992). Postsynaptic spike firing reduces synaptic $GABA_A$ responses in hippocampal pyramidal cells. *J Neurosci* **12**, 4122–4132.

Storm JF (1988). Temporal integration by a slowly inactivating K^+ current in hippocampal neurons. *Nature* **336**, 379–381.

Stuart G & Häusser M (1994). Initiation and spread of sodium action potentials in cerebellar Purkinje cells. *Neuron* **13**, 703–712.

Surmeier DJ, Stefani A, Foehring RC & Kitai ST (1991). Developmental regulation of a slowly-inactivating potassium conductance in rat neostriatal neurons. *Neurosci Lett* **122**, 41–46.

Turrigiano GG, Marder E & Abbott LF (1996). Cellular short-term memory from a slow potassium conductance. *J Neurophysiol* **75**, 963–966.

Wickens JR & Wilson CJ (1998). Regulation of action-potential firing in spiny neurons of the rat neostriatum *in vivo*. *J Neurophysiol* **79**, 2358–2364.

Wilson CJ (1995*a*). The contribution of cortical neurons to the firing pattern of striatal spiny neurons. In *Models of Information Processing in the Basal Ganglia*, ed. Houk JC, Davies JL & Beiser DG, pp. 29–50. MIT Press, Cambridge, USA.

Wilson CJ (1995*b*). Dynamic modification of dendritic cable properties and synaptic transmission by voltage-gated potassium channels. *J Comput Neurosci* **2**, 91–115.

Acknowledgements

We are grateful to Drs J.-M. Deniau and J. Glowinski for encouragement and helpful discussions. We thank Dr S. Slaght for critically reading the manuscript. We acknowledge support from the Fondation pour la Recherche Médicale and the Société de Secours des Amis des Sciences.